# VAGINAL INSERTED ESTRADIOL PHARMACEUTICAL COMPOSITIONS AND METHODS

## CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 14/521,230, filed Oct. 22, 2014, which claims priority to U.S. Provisional Patent Application Nos. 61/894,411, filed Oct. 22, 2013, and 61/932,140, filed Jan. 27, 2014, and which is a continuation-in-part of International Patent Application No. PCT/US2013/046443, filed Jun. 18, 2013, which claims priority to U.S. Provisional Patent Application No. 61/745,313, filed Dec. 21, 2012. All aforementioned applications are hereby incorporated by reference herein in their entirety.

## BACKGROUND

This application is directed to pharmaceutical compositions, methods, and devices related to hormone replacement therapy.

Postmenopausal women frequently suffer from atrophic vaginitis or vulvar and vaginal atrophy (hereinafter "vulvovaginal atrophy" or "VVA") with symptoms including, for example, vaginal dryness, vaginal odor, vaginal or vulvar irritation or itching, dysuria (pain, burning, or stinging when urinating), dysparuenia (vaginal pain associated with sexual activity), or vaginal bleeding associated with sexual activity. Other symptoms include soreness; with urinary frequency and urgency; urinary discomfort and incontinence also occurring ("estrogen-deficient urinary state(s)"). One symptom of vaginal atrophy is an increased vaginal pH, which creates an environment more susceptible to infections. The mucosal epithelium of the VVA patients also reported to show signs of severe atrophy and upon cytological examination accompanied by an increased number of the parabasal cells and a reduced number of superficial cells.

Each of these VVA-related states manifest symptoms associated with decreased estrogenization of the vulvovaginal tissue, and can even occur in women treated with oral administration of an estrogen-based pharmaceutical drug product. Although VVA is most common with menopausal women, it can occur at any time in a woman's life cycle.

Estrogen treatment has proven to be very successful in controlling menopausal symptoms, including vaginal atrophy (VVA). Several studies have shown that the symptoms connected with vaginal atrophy are often relieved by estrogen treatment given either systemically or topically. The existing treatments have numerous problems, for example compliance issues with patients not completing or continuing treatment due to the problems associated with the form of treatment.

Accordingly, disclosed herein is, among other things, a new soft gel vaginal pharmaceutical composition and dosage form containing solubilized estradiol for the treatment of VVA. The soft gel vaginal pharmaceutical composition has been designed to mitigate common limitations found with other vaginal forms of estradiol. The soft gel vaginal pharmaceutical composition is expected to ease vaginal administration, provide improved safety of insertion, minimize vaginal discharge following administration, and provide a more effective dosage form with improved efficacy, safety and patient compliance.

## SUMMARY

According to various aspects and embodiments of this disclosure, a soft gel vaginal pharmaceutical composition as a potential treatment for post-menopausal women suffering with moderate to severe symptoms of VVA is provided.

Provided herein is a pessary comprising: a) a therapeutically effective amount of estradiol; and b) a solubilizing agent comprising a medium chain oil.

In some embodiments, the pessary comprises about 1 μg to about 25 μg of estradiol. For example, the pessary can include about 1 μg to about 10 μg of estradiol; and about 10 μg to about 25 μg of estradiol.

In some embodiments, the estradiol is solubilized.

In some embodiments, the medium chain oil comprises at least one C6-C12 fatty acid or a glycol, monoglyceride, diglyceride, or triglyceride ester thereof.

In some embodiments, the solubilizing agent comprises at least one ester selected from the group consisting of: an ester of caproic fatty acid, an ester of caprylic fatty acid, an ester of capric fatty acid, and combinations thereof. For example, the solubilizing agent can include a caprylic/capric triglyceride.

In some embodiments, the pessary further comprises a capsule. For example, the capsule can be a soft gelatin capsule.

Also provided herein is a pessary comprising: a) a therapeutically effective amount of estradiol; b) a caprylic/capric triglyceride; c) a non-ionic surfactant comprising PEG-6 stearate and ethylene glycol palmitostearate; and d) a soft gelatin capsule.

In some embodiments, a pessary provided herein comprises about 25 μg of estradiol, wherein administration of the pessary to a patient provides, in a plasma sample from the patient: 1) a corrected geometric mean peak plasma concentration ($C_{max}$) of estradiol of about 19 pg/ml to about 29 pg/ml; and 2) a corrected geometric mean area under the curve $(AUC)_{0-24}$ of estradiol of about 75 pg*hr/ml to about 112 pg*hr/ml.

In some embodiments, a pessary provided herein comprises about 25 μg of estradiol, wherein administration of the pessary to a patient provides, in a plasma sample from the patient: 1) a corrected geometric mean peak plasma concentration ($C_{max}$) of estrone of about 9 pg/ml to about 14 pg/ml; and 2) a corrected geometric mean area under the curve $(AUC)_{0-24}$ of estrone of about 43 pg*hr/ml to about 65 pg*hr/ml.

In some embodiments, a pessary provided herein comprises about 25 μg of estradiol, wherein administration of the pessary to a patient provides, in a plasma sample from the patient: 1) a corrected geometric mean peak plasma concentration ($C_{max}$) of estrone sulfate of about 416 pg/ml to about 613 pg/ml; and 2) a corrected geometric mean area under the curve $(AUC)_{0-24}$ of estrone sulfate of about 3598 pg*hr/ml to about 5291 pg*hr/ml.

In some embodiments, a pessary provided herein comprises about 10 μg of estradiol, wherein administration of the pessary to a patient provides, in a plasma sample from the patient: 1) a corrected geometric mean peak plasma concentration ($C_{max}$) of estradiol of about 12 pg/ml to about 18 pg/ml; and 2) a corrected geometric mean area under the curve $(AUC)_{0-24}$ of estradiol of about 42 pg*hr/ml to about 63 pg*hr/ml. In some embodiments, the pessary further provides a corrected geometric mean time to peak plasma concentration ($T_{max}$) of estradiol of about 1 hrs to about 3 hrs.

In some embodiments, a pessary provided herein comprises about 10 μg of estradiol, wherein administration of the pessary to a patient provides, in a plasma sample from the patient: 1) a corrected geometric mean peak plasma concentration ($C_{max}$) of estrone of about 4 pg/ml to about 7